THE GRIGNARD REACTION APPLIED TO THE TERPENE SERIES

A THESIS
Submitted in partial fulfillment
of the requirements for the Degree
of Master of Science in Chemistry

by

Aurelius Franklin Chapman

Georgia School of Technology
Atlanta, Georgia
1938

49005

APPROVED:

ACKNOWLEDGMENT

THE AUTHOR WISHES TO EXPRESS HIS SINCERE APPRECIATION TO THOSE MEMBERS OF THE CHEMISTRY DEPARTMENT WHOSE KIND SUGGESTIONS AND CONSTRUCTIVE CRITICISM MADE THIS RESEARCH POSSIBLE, ESPECIALLY TO DR. W.S. TAYLOR, UNDER WHOSE DIRECTION THIS INVESTIGATION WAS CARRIED OUT.

TABLE OF CONTENTS

	PAGE
INTRODUCTION	1
HISTORICAL	2
PURIFICATION OF MATERIALS	7
PROCEDURE	8
CONCLUSION	14

THE GRIGNARD REACTION APPLIED TO THE TERPENE SERIES

INTRODUCTION

The purpose of this investigation was to extend the application of the Grignard reaction in the Terpene field. Bornyl chloride was selected as the alkyl halide to be used because it is a commercial product. A large number of compounds are theoretically possible by condensing bornyl magnesium chloride with various aldehydes and ketones. Since benzaldehyde can be easily purified, this substance was condensed with bornyl magnesium chloride.

In carrying out Grignard reactions of this type, complicated mixtures of substances are often obtained since the formation of a large number of isomeric compounds is possible. Since bornyl chloride and pinene hydrochloride seem to be identical, the word bornyl chloride has been substituted for pinene hydrochloride in the following discussion, some authors having used the term bornyl chloride; others, pinene hydrochloride. As a check on the literature, phenyl magnesium chloride was condensed with camphor, phenyl borneol being formed.

HISTORICAL

Houben and Kesselkaul[1] prepared the Grignard reagent from bornyl chloride and magnesium in absolute ether. When this product was treated with carbon dioxide, an acid, $C_{10}H_{17}COOH$, was obtained, which boils at 156 degrees C. at twelve m.m. of mercury pressure.

Nicolai Zilinsky[2] obtained camphane carboxylic acid, melting point 67 to 71 degrees C., by the treatment of bornyl iodide with magnesium and carbon dioxide. Small amounts of camphanewere found as a by-product.

In a later paper Houben[3] reported that camphane carboxylic acid has a melting point of 72 to 74° C. and boils at 153° C. at 13 m.m. pressure, or 268° C. under atmospheric pressure. Sodium and silver salts of the acid were obtained.

Sodium bornyl sulphinate, $C_{10}H_{17}SO_2Na.11(or12)H_2O$, was prepared by passing SO_2 into an ethereal solution of the magnesium compound of bornyl chloride and subsequently neutralizing the ether soluble portion with sodium carbonate. This compound[4]

(1) Joseph Houben and Ludwig Kesselkaul
Ber. 35, 3695-3696 (1902)
B.Chem abs. i page 42 (1903)

(2) Nicolai Zilinsky
Ber. 35, 4415-4419 (1902)
B.Chem abs. i page 185 (1903)

(3) J. Houben
Ber. 38, 3796-3801 (1905)
B.Chem abs. i page 21 (1906)

(4) Josef Houben and Hans Doescher
Ber. 39, 3503-3509 (1906)
B.Chem abs. i page 970-971 (1906)

crystallizes from water in well defined white leaflets having a faint characteristic odor. Bornyl sulphinic acid, when set free by sulphuric acid from the foregoing salt, separates as a colorless oil, slowly solidifying to needles on cooling in ice water; it melts at 64° C. and probably is hydrated.

Bornyl carbithionic acid[4], obtained by adding carbon disulphide to the ethereal solution of the magnesium compound of bornyl chloride, is a brown oil having a camphor like odor; it is extremely unstable but yields characteristic metallic salts. The action of sulphur on bornyl magnesium chloride leads to the production of thioborneol together with small amounts of dibornyl and bornyl disulphide.

Josef Houben and Hans Doescher[5] obtained hydropinenealdehyde by boiling methyl formanilide for eight hours with bornyl magnesium chloride. Hydropinenealdehyde was isolated by the formation of its sodium hydrogen sulfite addition product. The aldehyde has the odor of camphor and undergoes oxidation very readily, being very volatile with steam. Its melting point was reported as being above 120° C., no special melting point being given because of its rapid oxidation.

Hess[6] made an attempt to prove that pinene hydrochloride is bornyl chloride and camphene hydrochloride is iso-bornyl chloride.

(4) Josef Houben and Hans Doescher
Ber. 39, 3503-3509 (1906)
B.Chem abs. i page 970-971 (1906)

(5) Josef Houben and Hans Doescher
Ber. 40, (4576-4579), (1907)
B.Chem abs. i page 27 (1908)

(6) Albert Hess
Ber. 39, 1127-1155
B.Chem abs. i page 375 (1906)

Attempts to bring about the inter-action of pinene or camphene hydrochloride with magnesium using the ordinary catalytic agents (iodine, aluminum chloride, and alkyl halides) were unsuccessful. By adding the hydrochloride dissolved in a benzene and ether mixture to magnesium while the latter is reacting vigorously with ethyl bromide dissolved in ether, a magnesium compound, $C_{10}H_{17}MgCl$, is produced. With pinene hydrochloride a yield of 20% to 85% of the Grignard reagent was reported. Ten to fifteen per cent of dibornyl, $(C_{10}H_{17})2$, which was crystallized from acetic acid and had a melting point of 85° to 87° C., was also reported, small quantities of camphene and camphane being formed as by-products. With camphene hydrochloride 60% of the Grignard reagent and 20% of a dibornyl, $C_{20}H_{34}$, were obtained. The compound, $C_{20}H_{34}$, was reported as having a melting point of 90° C. Inactive camphane was produced by decomposing the Grignard reagent formed from either camphene hydrochloride or pinene hydrochloride with water. When air was bubbled into the ethereal solution of pinene magnesium chloride and the resulting product decomposed with acid, a 60% to 65% yield of borneol was reported. The remainder of the product consisted principally of a dibornyl, melting point 85° C. Cases were reported in which a yield of 5% to 8% of iso-borneol was produced. This was probably due to the fact that camphene hydrochloride was present in the pinene hydrochloride as an impurity. On oxidizing the magnesium derivative of camphene hydrochloride in a like manner, 15% iso-borneol, 30% borneol, and 21% of dibornyl (melting point 90° C.) were produced. According to Hess, this shows that either a large amount of pinene magnesium chloride is

produced or that during oxidation of the Grignard reagent an isomeric change or changes occur.

G. Vavon and A. L. Berton[7] report that when bornyl chloride is treated with magnesium and the resulting Grignard reagent oxidized, a mixture of borneol and iso-borneol is produced. The amount of each of these substances produced is reported as depending upon the temperature of the oxidation.

Rene Bousset and Mille. M. Vaugin[8] allowed one mole of bornyl chloride to react with magnesium, and 0.6 moles of ethyl formate were added. The reaction was carried out at -20° C. in an atmosphere of nitrogen. The crude product (147g.) gave 49 grams of esters, 15 grams of the desired alcohol, 36 grams of bornylene, 15 grams of camphane, and 32 grams of dibornyl.

Under the operating conditions given, the action of one mole of ethyl formate on two moles of the Grignard reagent may be considered as giving one mole of $C_{10}H_{16}$ and one mole of $C_{10}H_{17}CH_2OMgCl$. The reaction used 68% of the initial salt, giving an alcohol $C_{10}H_{17}CH_2OH$ with a yield of 34%.

R. Bousset[9] also treated bornyl magnesium chloride with ethylene oxide. The reaction was carried out in absolute ether at -10° C. The temperature was gradually raised, and di-ethyl ether replaced by butyl ether. Camphanyl ethyl alcohol was

(7) G. Vavon and A. L. Berton
Compt. rend., 175, 369-372, (1922)
B.Chem abs. i 1943-1944 (1922)

(8) Rene Bousset and Mille. M. Vaugin
Bull. soc chim.
(4), 47, 986-1003 (1930)
Abs. J. Am. Chem Soc page 507 (1931)

(9) R. Bousset
Bull. Soc Chim. (1934), (V), 1, 1305-1307
B.Chem abs. A. page 219 (1935)

formed, boiling point 135° - 136° C. at 17 m.m. of pressure. The melting point was reported as being 25° C. The alcohol was isolated as its hydrogen phthalate, melting point 155° C.

(10)
Rene Bousset reports that when bornyl chloride, in absolute ether, is allowed to react with magnesium, and the resulting Grignard reagent treated with phthalic anhydride at 0° C., an 80% yield of ortho camphane 2-carboxyl benzoic acid, melting point 154° C., is produced.

(11)
Methyl and ethyl borneol have been prepared by the action of methyl and ethyl magnesium halide on camphor. There was some difficulty in the preparation of propyl borneol, however. When propyl magnesium bromide is allowed to react with camphor, (12)
allyl borneol is produced in an 85% to 95% yield in the place (12)
of propyl borneol. Allyl borneol can be reduced, however, to give propyl borneol, boiling point 118° C., melting point 30-32° (13)
C. Phenyl borneol has been obtained from camphor and phenyl magnesium bromide in absolute ether. The yield was reported as being 20% to 30%, some diphenyl being formed as a by product. Phenyl borneol, according to the literature, has a boiling point

(10) Rene Bousset
Bull. Soc Chim (5), 2, 2182-7; 3, 318-19, (1936)
Abs. J. Am. Chem Soc. page 1776 (1936)

(11) Ber., 34, 2883 (1901)

(12)a Letschislav Cohojn
J. Russ. Phys. Chem. Soc., 44, 1844-1853 (1912)

(12)b S. S. Nametkin and A. I. Schawrigin
Ann. 516, 199-217 (1935)
Abs. J. Am. Chem Soc., 29, 3669

(13) S. S. Nametkin, H. S. Kichkina, and D. N. Kursanov
J. Russ. Phys Chem. Soc. 61, 1065, 79 (1929)
Abs. J. Am. Chem. Soc. page 841 (1930)

of 173-174° C. at 16-17 m.m. pressure.

PURIFICATION OF MATERIALS

Some difficulty was experienced in the obtaining of dry, alcohol-free ether. The ordinary commercial ether contained considerable quantities of alcohol; therefore, it was necessary to remove this impurity before the ether could be purified sufficiently for the use in Grignard reactions.

The ether used was purified as follows:
Equal quantities of ordinary commercial ether and water were shaken thoroughly. Next the water was drawn off and an equal amount of fresh water added with further shaking. This procedure was repeated until the ether had been shaken with six fresh portions of water. The ether is next placed over anhydrous calcium chloride and allowed to stand for several days, then placed over bright, clean sodium, and allowed to stand over night. The ether was then distilled, the first and last fractions being rejected.

The camphor used was the ordinary commercial gum variety obtained from Coleman & Bell.

The bornyl chloride used in this investigation was a gift from DuPont. It was sublimed twice, a large funnel being used as a sublimator.

Both benzaldehyde and brombenzene were purified by distillation.

Bright magnesium shavings (labeled "Grignard") or ribbon were used.

In the following experiments, iodine, brombenzene, and

ethyl bromide were used as catalysts for the Grignard reaction. An attempt to use diethyl sulfide as a positive catalyst failed. Diethyl sulfide seemed to retard the action of brombenzene and magnesium. A yellow-red substance, which was doubtless sulfur from the decomposition of the sulfide, appeared when brombenzene mixed with ether and diethyl sulfide was brought in contact with magnesium.

PROCEDURE

Twenty grams of bornyl chloride, dissolved in 250-300 c.c. of absolute ether, were placed in a one liter round bottom flask fitted with a reflux condenser and drying tube. A very slight excess of magnesium ribbon and a few c.c. of brombenzene were added. After a crystal of iodine had been added, a slight reaction began. The heat from a 60 watt electric light bulb, fastened several inches below the flask was sufficient to cause the solution to boil. In a short time a white solid appeared around the residual magnesium in the flask. On further heating, this solid dissolved. After heating for several hours, the mixture was cooled in an ice bath, and the calculated amount of benzaldehyde, dissolved in a few c.c. of absolute ether, was slowly added, the solution being agitated during the addition. A white solid formed as soon as the benzaldehyde came in contact with the solution. When all the benzaldehyde had been added, the mixture was refluxed for 15-20 minutes. Next the mixture was cooled and sufficient ice added to decompose the Grignard reagent. Then enough hydrochloric acid was added to dissolve the basic salt of magnesium formed. The ether layer was separated,

shaken with sodium carbonate solution, and dried over anhydrous calcium chloride. Next the ethereal solution was filtered, to remove any suspended calcium chloride, and the ether removed by distillation. A sweet smelling, thick, yellow oil remained in the flask. Even a dry ice ether mixture failed to freeze the oil. Attempts to esterify the oil with benzoyl chloride and para nitro benzoyl chloride failed. A small amount of white crystalline solid, melting point 153° C., was obtained. This was probably camphane, melting point 153° C. This could be accounted for by the hydrolysis of bornyl magnesium chloride that did not condense with benzaldehyde.

Next a twenty gram run of bornyl chloride dissolved in 250-300 c.c. absolute ether, and an excess (three times the calculated amount) of activated magnesium, was carried out in a manner similar to that outlined above. In this case, the mixture was refluxed from seven to eight hours, then cooled and the Grignard reagent poured into another flask. Twenty grams of bornyl chloride in 250-300 c.c. of absolute ether were added to the unused magnesium in the flask. Enough magnesium (3 g.) was added to compensate for that probably used to form the Grignard reagent. The mixture was then allowed to react for about 16-17 hours (over night), heat being applies for about four to five hours. Next the Grignard reagent was poured off and another day run made as outlined above. This procedure was continued until four day and three night runs had been made. The day and night runs were kept in separate containers. Of course the Grignard reagent was condensed with benzaldehyde as soon as it was poured off the unused magnesium after each run.

The mixtures of oils were worked up in a manner similar to that outlined above with the exception that the residual benzaldehyde was removed by treating the ether layers with a few c.c. of 40% sodium bisulfite solution. The ether layers were then shaken with sodium carbonate solution, separated, and dried over calcium chloride. After the ether had been removed by distillation, a thick yellow oil was obtained from both day and night runs. The average yield of complex oils for the day runs was 16 c.c. per 20 g. of bornyl chloride used; for the night runs the average was 14 c.c. per 20 g. of bornyl chloride used.

The oil fractions from the day and night runs were placed in one flask and subjected to distillation at reduced pressure. A pressure regulator, which was designed by Professor H. M. Waddle of this Department, was used to keep the pressure constant during the distillation. By use of his regulator, it was possible to keep the pressure practically constant, the variation never being over one m.m. of mercury. This distillation was carried out at a pressure between one and two m.m. At the beginning of the distillation a white solid, approximately 50 g., distilled over. This solid had the physical properties of unchanged bornyl chloride. On further distillation at a pressure of one to two m.m., 50 c.c. of clear, colorless oil were obtained between 50 and 90° C. The next fraction came over between 121-125° C. at 1-2 m.m. On cooling with ice and concentrated hydrochloric acid a white solid (6 grams) separated. After four crystallizations from 95% alcohol, and one from glacial acetic acid, the solid had a melting point of 89-90° C., molecular weight by freezing point lowering method, in benzene solution, 285. This checks

fairly close for dibornyl as reported by Hess[6], melting point 90°C., molecular weight 274. The last fraction, a yellow oil, came over between 183 and 184.5° C. at a pressure of 1 to 2 m.m., yield 2 or 3 c.c. An attempt to esterify this oil failed, indicating the absence of the desired alcohol, phenyl bornyl carbinol.

The first fraction was redistilled. Fraction #1 came over at 70 to 70.4° C. at 3 m.m. pressure; fraction #2, 79-80° C.; fraction #3, 81-82° C.; fraction #4, 83-84° C.; fraction #5, 94-95° C. An attempt was made to esterify each fraction with para nitro benzoyl chloride. In each case a white solid separated, which after several crystallizations from 95% alcohol had a melting point of 84-85° C., molecular weight 283. This corresponds to an isomeric dibornyl as reported by Hess[6], melting point 85° C., molecular weight 274. The total yield of this substance from all fractions was approximately 35 g.

Next 45 g. of bornyl chloride and 29 g. of ethyl bromide dissolved in absolute ether were allowed to react with magnesium shavings. The resulting Grignard reagent was condensed with 58 g. of benzaldehyde. The product was worked up in the usual way. The result was, in general, the same as that outlined above. The same two isomeric dibornyls were the only products separated from the complex mixture of oils obtained. A test for unsaturation was obtained from the lower boiling oil fraction, potassium permanganate being decolorized by the oil. If the secondary alcohol, phenyl bornyl carbinol, had been formed when

(6) Albert Hess
Ber. 39, 1127-1155
B. Chem abs. 1 page 375 (1906)

benzaldehyde was condensed with bornyl magnesium chloride, it may have decomposed to form water and an unsaturated compound.

Thirty-five g. of bornyl chloride and activated magnesium (in slight excess) were refluxed for several days. The Grignard reagent was cooled and ice added, hydrochloric acid being added to dissolve the basic magnesium salt formed. Then the ether layer was separated, shaken with sodium carbonate solution, and dried over anhydrous calcium chloride. After the ether was removed by distillation, a complex oil mixture remained. The only product isolated by a fractional distillation at 3 m.m. pressure was diborryl.

Eighty grams of brombenzene, dissolved in approximately 300 c.c. of absolute ether, were allowed to react with an excess of magnesium. The solution was cooled from time to time in order to avoid the formation of diphenyl. After the vigorous reaction ceased, the solution was heated on a water bath for about fifteen minutes, cooled, and gum camphor dissolved in absolute ether was added. The camphor did not seem to react with the Grignard reagent as rapidly as benzaldehyde did. When the addition of camphor was complete, the condensation mixture was refluxed for about 15-20 minutes, cooled in an ice bath, and crushed ice added. Enough hydrochloric acid was added to dissolve the basic magnesium compound formed. The ether layer was separated, shaken with sodium carbonate solution, and dried over calcium chloride. The ether-oil solution was next filtered and the ether removed by distillation. A thick yellow, complex mixture of oils remained in the flask. The oil was distilled at 16-17 m.m. of mercury pressure. At the beginning of the distillation the unused

camphor sublimed into the delivery tube causing trouble. The first fraction came over at 165-172° C. The next fraction (largest) came over at a temperature of 173-174° C. at 16-17 m.m. This is the boiling point of phenyl borneol as recorded in the literature.(13) Hence this substance was doubtless phenyl borneol, a tertiary alcohol, yield fifteen grams.

An attempt was made to nitrate the two isomers of dibornyl. The first attempt was made upon the lower melting isomer. Two grams of dibornyl dissolved in 16 c.c. of glacial acetic acid were allowed to come in contact with 1 c.c. of concentrated nitric acid and 2 c.c. of acetic anhydride. The solution was heated at 45° C. for one hour. The dibornyl remained unchanged. Now approximately 2 g. of dibornyl were heated with 22 c.c. of concentrated nitric acid and 2 1/2 c.c. of concentrated sulfuric acid for about twenty minutes at a temperature of 125° C. The product was poured into ice water and the white solid crystallized from boiling water. Beautiful crystals were obtained, melting point 234-235° C. (uncorrected), yield approximately 50%. A test for nitrogen failed to show the presence of a nitro compound. The molecular weight obtained from the substance's neutralization equivalent showed that the substance was doubtless a dicarboxylic acid derivative of dibornyl. The acid is soluble in alcohol (95%), acetone, and glacial acetic acid. It is insoluble in carbon disulfide, carbon tetra chloride and benzene. The acid dissolves in sodium hydroxide to give a beautiful red solution. On the

(13) S. S. Nametkin, H. S. Kichkina, and D. N. Kursanov J. Russ. Phys Chem. Soc. 61, 1065, 79 (1929) Abs. J. Am. Chem. Soc. page 841 (1930)

addition of hydrochloric acid, the free acid is obtained which has a slight yellow tint. No amount of boiling with carbon black would remove the color from this acid. The color was doubtless due to a small amount of oxidation product. The calcium and barium salts of the acid are soluble in water since no precipitation occurred when a calcium or barium salt was added to a hot solution of the acid.

The other isomeric dibornyl, melting point 89-90° C., was treated in a similar manner, but the dibornyl remained unchanged. Next 2.5 g. of the substance was treated with 30 c.c. of fuming nitric acid and 5 c.c. of concentrated sulfuric acid. The temperature was kept between 80 and 90° C., for twenty minutes. Under these conditions, the dibornyl remained unchanged. With a 50-50 mixture of concentrated sulfuric and fuming nitric acids, the dibornyl decomposed, but no nitro or oxidation product could be isolated. This isomer can be oxidized with potassium dichromate and sulfuric acid, potassium permanganate and alkali or acid, or aqua regia. On examining the mixture after oxidation, some unchanged dibornyl was the only product isolated.

CONCLUSION

The Grignard reagent of bornyl magnesium chloride was prepared in ethereal solution. On condensing bornyl magnesium chloride with benzaldehyde, no secondary alcohol was isolated, because of the complex nature of oils formed in the reaction. Since a test for unsaturation was obtained, the secondary alcohol doubtless lost water during the condensation to give an olefin.

Phenyl borneol was prepared from phenyl magnesium chloride and camphor, the boiling point checking with that in the literature.[13]

An attempt was made to nitrate the two isomeric dibornyls, no nitro products being isolated. The lower melting isomer was oxidized to a dicarboxyllic acid in approximately 50% yields. No definite oxidation products were isolated from the oxidation of the higher melting isomer.

(13) S. S. Nametkin, H. S. Kichkina, and D. N. Kursanov J. Russ. Phys Chem. Soc. 61, 1065, 79 (1929 Abs. J. Am. Chem. Soc. page 841 (1930)